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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	37

DATE MAILED: 07/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/220,691	TSUJI ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1,3,4,6 and 22*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Int. Sum. paper # 34 attached.*

Jon P Weber, Ph.D.
Primary Examiner
Art Unit: 1651

Status of the Claims

The Request for Reconsideration filed 27 June 2003 has been received and entered. Claims 1, 3-4, 6 and 22 have been presented for examination.

Claim Rejections - 35 USC § 112

Claims 1, 3-4, 6 and 22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibitors of elastase-like enzymes, does not reasonably provide enablement for inhibitors of elastase-like enzymes or neutral endoproteases that are not inhibitors of matrix metalloproteases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

It is argued that phosphoramidate compounds are disclosed at page 5 that indicate the general structure of the preferred embodiments. It is argued that in example 1, a phosphoramidate compound was found that inhibits elastase and neutral endoprotease, but does not inhibit MMP. Several specific phosphoramidate inhibitors are provided in examples 1-6. It is commented that none of the references cited in the Office action of 27 February 2003, hence these references are alleged to not be relevant to the instant claims. It is argued that numerous compounds are known and shown in the cited references that inhibit MMP. Accordingly it is urged that it is not undue burden to determine if these compounds meet the claim limitations. It is argued that *Hybritech Inc. v Monoclonal Antibodies, Inc.* is relevant as an analogous fact pattern because instantly classes of suitable inhibitor compounds and relevant assays are presented. This case indicates that some experimentation is acceptable.

The *Hyritech* case does not change the question posed by the *Wands* factors. Does the instant disclosure provide sufficient showing and teaching so that undue experimentation is not necessary? The emphasis here is not just on experimentation or the quantity of experimentation, but whether the experimentation is undue.

Consider the claims as presented. Claim 1 broadly asserts any inhibitor of elastase or neutral endoprotease that does not inhibit MMP so long as it is not mercaptoproprionamide. Claims 3, 4, and 6 do not change this. Claim 22 limits the inhibitor to phosphoric acid compounds or derivatives. None of the claims are directed to phosphoramidates as argued. The closest is claim 22 if one considers phosphoramidates to be the inhibiting "derivatives" of phosphoric acid envisaged (not immediately apparent). Hence, the art cited in the Office action of 27 February 2003 is relevant to all of the instant claims. The request seems to believe that the claims are limited by the disclosure of preferred embodiments to phosphoramidates. While claims must be "given the broadest reasonable interpretation consistent with the specification", "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from `reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." *In re Prater*, 162 USPQ 541, 550 -51 (CCPA 1969). This is impermissible importation of subject matter from the specification into the claim. Accordingly, the universe of potential inhibitors of elastase and neutral endoproteases is vastly broader than either argued or disclosed.

Consider now that each of these potential inhibitors of elastase and neutral endoproteases would have to be screened to determine if they inhibited MMPs. If there were a discrete number

of such compounds, even though there were many of them, it could possibly be considered routine experimentation to screen the compounds. In the instant case, there are an unlimited number of potential inhibitors that must be screened. There is only one disclosed compound that can meet the claim limitations. There is not even a clear expectation that the compounds disclosed in examples 2-6 will meet the claim limitations. All one can say is that these compounds are likely inhibitors because of their structural similarity to known inhibitors. It cannot be said that they will have the claimed selectivity.

Proteases cleave a polymeric structure, so typically, the active/binding sites are extended. Hence, it is well known in the art of protease enzymology, that the protease active sites not only have catalytic groups at positioned to cleave the sissile bond, but there are subsites for substrate and product recognition, especially the S1′ and P1′ subsites. It is the goal to describe and delineate the nature of the differences in these subsites to provide the desired selectivity between different enzymes. Normally, structural information about the enzyme's subsites is needed, but it is possible to map the properties of the subsites by means of SAR studies. The classic work of Cushman and associates in mapping the angiotensin converting enzyme (ACE) site to design carboxypeptidase-like inhibitors of ACE comes to mind. This history of the state of the art raises two questions. 1) Does the instant disclosure provide guidance on the structure of the subsites? 2) Are SAR studies presented that allow a person of ordinary skill in the art to map the properties of the subsites absent structural information? The answer to both of these questions is no. Clearly there is no structural information presented. There is also no consistent data presented which allows a person of ordinary skill in the art to map the subsites.

Most investigators seeking selective inhibitors between two enzymes with closely related activities are satisfied with a 100 to 500-fold selectivity because this is the minimum necessary for an effective selectivity. In the instant case, extreme selectivity between elastase and neutral endoproteases versus MMPs is claimed. The inhibitor should inhibit elastase and neutral endoproteases but not the MMP at all.

Considering the number of inhibitors that must be screened, the lack of guidance on selecting suitable structures and the considerable uncertainty in the ability to find inhibitors that would meet the stringent claim limitations, the conclusion of undue experimentation is justified. The purpose of this requirement is to limit patent protection to inventions that possess a certain level of "real world" value, as opposed to subject matter that represents nothing more than an idea or concept, or is simply a starting point for future investigation or research; a patent is not a "hunting license" (*Brenner v. Manson*, 383 U.S. 519, 528-36, 148 USPQ 689, 693-96).

Applicant's arguments filed 27 June 2003 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 112, first paragraph is adhered to for the reasons of record and the additional reasons above.